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Attorney Docket No. 22596-536 PRO B

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR § 1.53(c)

INVENTORS / APPLICANTS			
Given Name (last name, first name, and middle initial [if any])			Residence (City and State or Foreign Country)
Müller	Klaus		Münster, Germany
Sellmer	Andreas		Lappersdorf, Germany
Salvesen	June		79 Cameron Drive, Marlborough, MA 01752

☐ Additional inventors are being named on page 2 attached hereto

TITLE OF THE INVENTION

Novel Lapacho Compounds and Methods of Use Thereof

CORRESPONDENCE ADDRESS

Attorney Name: Firm Name and Address:	Ivor R. Elrifi MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C. One Financial Center Boston, MA 02111
Telephone:	(617) 542-6000
Fax:	(617) 542-2241

ENCLOSED APPLICATION PARTS

☒ Specification — Number of Pages: 22 pp.
☒ Drawings (☐ Formal; ☒ Informal) — Number of Sheets: 3 pp.
☐ Other documents (specify):

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government:

☐ No.
☐ Yes

METHOD OF PAYMENT

☒ A check in the amount of $160.00 is enclosed to cover the filing fees of the Provisional application.
☐ The Commissioner is hereby authorized to charge $160.00 to cover the filing fees of the Provisional application to Deposit Account No. 50-0311, Reference No. 22596-536 PRO B.
☒ The Commissioner is hereby authorized to charge additional fees or credit any overpayment to Deposit Account No. 50-0311, Reference No. 22596-536 PRO B.

Respectfully submitted,

Dated: January 21, 2003

Ivor R. Elrifi, Reg. No. 39,529
Barry J. Marenberg, Reg. No. 40,715
MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C.
One Financial Center
Boston, MA 02111
Telephone: (617) 542-6000

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Date of Deposit: January 21, 2003

Attorney Docket No. 22596-536 PRO B

NOVEL LAPACHO COMPOUNDS AND METHODS OF USE THEREOF

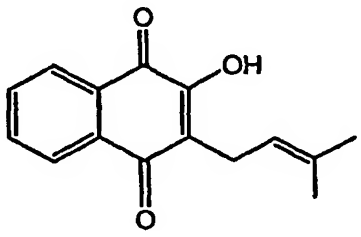
RELATED APPLICATIONS

This application claims priority from U.S.S.N. 60/411,478, filed September 17, 2001, which is incorporated by reference in its entirety.

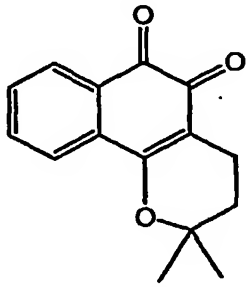
BACKGROUND OF THE INVENTION

Lapacho ("pau d'arco", "ipê-roxo", "taheebo") is a commercial natural product obtained from the bark of *Tabebuia* trees, and in particular from *T. impetiginosa* (Martius ex DC.) Standley (Binoniaceae), which are found in the rainforests throughout Central and South America. Lapacho has been used as a folk medicine for many years, in particular for the treatment of cancer (Hartwell, J. L., Lloydia, 31, 71-170, 1968) and disorders of the immune system, including psoriasis (Jones, K., Pau D'arco: Immune Power from the Rain Forest; Healing Arts Press; Rochester, Vermont, 1995).

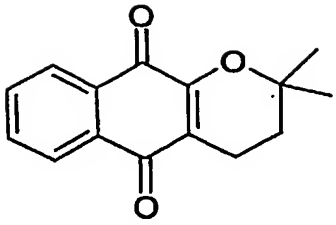
The occurrence of naphthoquinones in various members of the genus *Tabebuia* has been widely reported (Burnett, A.R., et. al., J. Chem. Soc., C, 2100-2104, 1967; Rao, M.M, et. al, J. Nat. Prod., 45, 600-604, 1982; Girard, M., et. al., J. Nat. Prod., 51, 1023-1024, 1988; and Diaz, F., et. al., J. Nat. Prod., 59, 423-424, 1996). The best known of these compounds are lapachol, alpha-lapachone (α-lapachone) and beta-lapachone (β-lapachone), which have the following chemical structures:



Lapachol



Beta-Lapachone



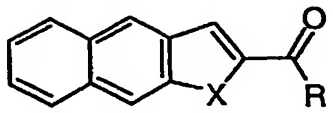
Alpha-Lapachone

Although all three of these compounds have been reported to have antiproliferative activity, β-lapachone, in particular, has demonstrated significant antineoplastic activity against a wide spectrum of human cancer cell lines at concentrations typically in the range of 1-10 μM (IC_{50}). For example, the cytotoxicity of β-lapachone has been demonstrated in transformed cell lines derived from patients with promyelocytic leukemia (Planchon *et al.*, *Cancer Res.*, 55 (1996) 3706), prostate (Li, C.J., *et al.*, *Cancer Res.*, 55 (1995) 3712), malignant glioma (Weller, M. *et al.*, *Int. J. Cancer*, 73 (1997) 707), hepatoma (Lai, C.C., *et al.*, *Histol Histopathol*, 13 (1998) 8), colon (Huang, L., *et al.*, *Mol Med*, 5, (1999) 711), breast (Wuertzberger, S.M., *et al.*, *Cancer Res.*, 58 (1998) 1876), ovarian (Li, C.J. *et al.*, *Proc. Natl. Acad. Sci. USA*, 96(23) (1999) 13369-74), pancreatic (Li, Y., *et al.*, *Mol Med*, 6 (2000) 1008; Li, Y.Z., *Mol Med*, 5 (1999) 232), and multiple myeloma cell lines, including drug-resistant lines (Li, Y., *Mol Med*, 6 (2000) 1008). No cytotoxic effects were observed on normal fresh or proliferating human PBMC (Li, Y., *Mol Med*, 6 (2000) 1008).

Other lapacho-derived compounds have been shown to have antiproliferative activity. Eight compounds, representing the most common constituents of the inner bark of *T. impetiginosa* and including lapachol, α-lapachone and β-lapachone, were evaluated for antiproliferative and cytotoxic activity in the nontransformed human keratinocyte cell line HaCaT, a model for the highly proliferative epidermis characteristic of psoriasis (Müller, K., *et al., J. Nat. Prod.* 62 (1999) 1134-1136). While lapachol and α-lapachone were relatively inactive in this model, β-lapachone and several naphtho[2,3-b]furan diones displayed inhibition of keratinocyte growth comparable to the antipsoriatic drug anthralin. These findings encourage the design and synthesis of new lapacho compounds and their evaluation for antiproliferative activity in a variety of biological systems.

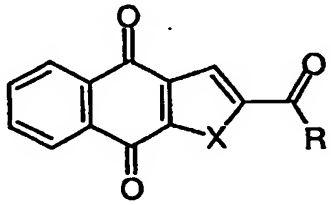
DESCRIPTION OF THE INVENTION

The present invention concerns new synthetic lapacho derivatives of Formula I:



I

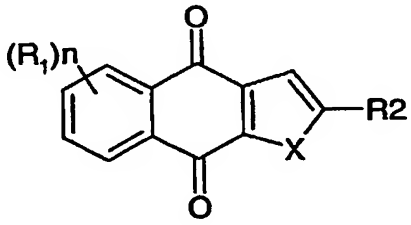
or Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein X is O or S; and R is straight-chained or branched alkyl containing 1-6 carbons, aryl, substituted aryl (substituted, for example, with: hydroxyl, alkoxy, alkyl, nitro, halogen carboxyl, carboxyalkyl), or straight-chained or branched alkylaryl.

The present invention also concerns new synthetic lapacho analogs of Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein X is O or S; R_1 is independently at each incidence hydrogen, hydroxyl, alkoxyl, alkyl of 1-6 carbons, nitro, halogen, carboxyl or carboxyalkyl; R_2 is hydrogen, acyl, straight-chained or branched alkyl containing 1-6 carbons or carboxyalkyl; and n is 0, 1 or 2.

Preferred compounds of Formula I are those in which X is S and R is aryl or substituted aryl.

Preferred compounds of Formula II are those in which X is O or S and R is alkyl, aryl or mono- or di-substituted aryl.

Preferred compounds of Formula III are those in which X is S, R_1 is hydroxyl or alkylcarbonyl, R_2 is hydrogen, and n is 1 or 2.

The most preferred compounds of the invention are shown in Figures 1, 2 and 3.

The present invention also provides pharmaceutical formulations comprising a compound of Formula I, II or III in combination with at least one pharmaceutically acceptable excipient or carrier.

The present invention also provides a method for the treatment of cell proliferative disorders in mammals comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, II or III. The invention further provides the use of a compound of Formula I, II or III for the preparation of a medicament useful for the treatment of a cell proliferative disorder.

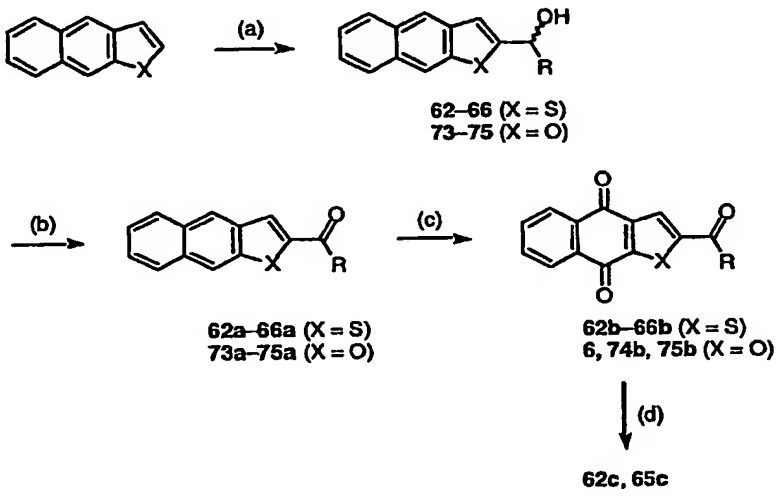
As used herein, the term "cell proliferative disorder" refers to conditions in which the unregulated and/or abnormal growth of cells can lead to the development of an unwanted condition or disease, which can be cancerous or non-cancerous, for example a psoriatic condition. As used herein, the term "psoriatic condition" refers to disorders involving keratinocyte hyperproliferation, inflammatory cell infiltration, and cytokine alteration.

In addition to psoriatic conditions, the types of proliferative diseases which may be treated using the compositions of the present invention are epidermic and dermoid cysts, lipomas, adenomas, capillary and cutaneous hemangiomas, lymphangiomas, nevi lesions, teratomas, nephromas, myofibromatosis, osteoplastic tumors, and other dysplastic masses and the like.

The process used for the preparation of most preferred compounds of Formula I and II is shown in Scheme 1. Introduction of the 2-acyl functionality onto the naphtho[2,3-*b*]thiophene and naphtho[2,3-*b*]furan nuclei was achieved by metalation with *sec*-butyllithium in the presence of tetramethylethylenediamine, where substitution occurs exclusively in the 2-position. The reaction of naphtho[2,3-*b*]thiophene- and naphtho[2,3-*b*]furan-2-yl-lithium with the appropriate aldehydes gave the secondary alcohols **62–66** and **73–75**, respectively. The desired acyl group was obtained by oxidation of the alcohol group with activated manganese(IV) oxide in

methylene chloride. Oxidation of the 2-acyl analogues with chromium trioxide in glacial acetic acid provided the corresponding naphtho[2,3-*b*]thiophene- and naphtho[2,3-*b*]furan-4,9-diones **62b–66b** and **6,74b,75b**, respectively. The phenolic analogues **62c** and **65c** were obtained by ether cleavage of the corresponding methyl ethers **62b** and **65b** with boron tribromide in methylene chloride.

Scheme 1

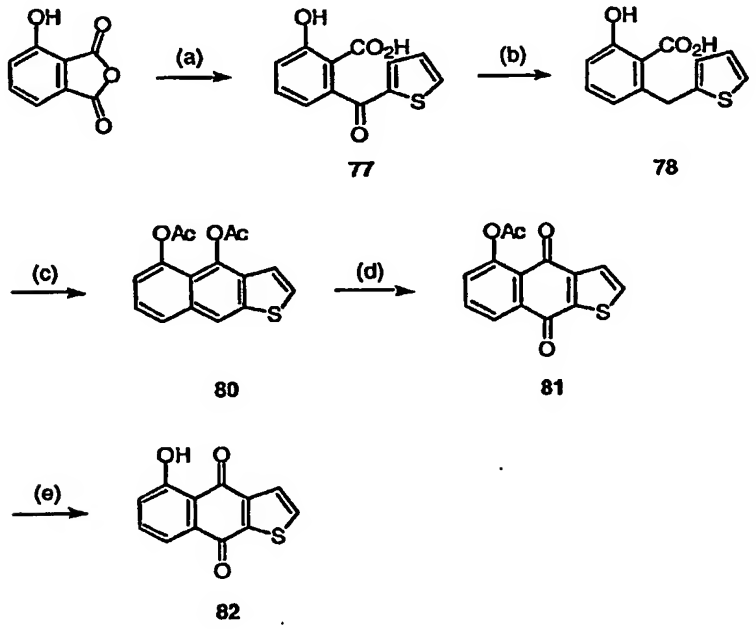


Reagents: (a) *sec*-BuLi, tetramethylethylenediamine, ether, -78 °; (b) MnO_2, CH_2Cl_2; (c) CrO_3, HOAc; (d) BBr_3, CH_2Cl_2. R and X are defined in Figures 1 and 2.

The process used for the preparation of most preferred compounds of Formula III is shown in Scheme 2. An aluminum chloride catalyzed Friedel-Crafts acylation of thiophene with 3-hydroxyphthalic anhydride in methylene chloride afforded exclusively 2-hydroxy-6-(2-thenoyl)-benzoic acid (77), which was formed by the reaction of the non-hydrogen-bonded carbonyl group with thiophene. Structural proof of 77 was given by reduction with zinc in aqueous ammonia to 2-hydroxy-6-(2-thenyl)-benzoic acid (78), which in turn was converted to the corresponding methyl 2-methoxy-6-(2-thenyl)-benzoate and identified by its NOESY spectrum. Ring closure of 78 with zinc chloride in glacial acetic acid and acetic anhydride to

naphtho[2,3-b]thiophene 80 proceeded with concomitant acetylation of the oxygen functions. On oxidation with chromium trioxide it afforded the quinone 81, and hydrolysis of the acetoxy function with sodium hydroxide gave the phenolic analogue 82.

Scheme 2



Reagents: (a) thiophene, $AlCl_3$, CH_2Cl_2; (c) Zn, NH_3, Δ; (c) Ac_2O, HOAc, $ZnCl_2$, Δ; (d) CrO_3, HOAc; (e) 6 N NaOH, Δ.

Compounds of the present invention have demonstrated potent antiproliferative activity against the nontransformed human keratinocyte line HaCaT, as demonstrated by reduction in cell number over time as compared to control plates. Anthralin, an antipsoriatic drug, was used as a positive control. Antiproliferative activity was measured directly by counting the dispersed cells under a phase-contrast microscope. Table 1 shows the concentrations of the compounds required to inhibit 50% of cell growth (IC_{50}). The cytotoxicity of naphthoquinones has been thought to

result, at least in part, from reactive oxygen species, generated during redox cycling between the quinine and reduction products (Munday, R., Free Radic. Biol. Med., 22, 689-695, 1997), which cause peroxidative damage to membrane lipids. To assess the correlation of keratinocyte growth inhibition with membrane damage, the release of lactate dehydrogenase from the treated cells was also quantitated.

Table 1. Antiproliferative activity and cytotoxicity of synthetic lapacho analogs

Compound	X	R	R1	R2	AA[a] in HaCaT Cells IC_{50} (μM)	LDH[b] (mU)	AA[c] in Cancer Cell Lines IC_{50} (μM)		
							DLD1	SW480	MCF7
Compounds of Formula I									
73a	O	Me	NA	NA	> 5	ND	>32	>32	>32
74a	O	Ph	NA	NA	1.9	142	7.6	12	≤1
75a	O	3,4-$(OMe)_2$-Ph	NA	NA	> 5	ND	14	30	12
63a	S	Me	NA	NA	5.0	ND	>32	>32	>32
64a	S	Ph	NA	NA	0.3	122	1.5	≤1	≤1
62a	S	4-OMe-Ph	NA	NA	> 5	ND	>32	>32	>32
65a	S	3,4-$(OMe)_2$-Ph	NA	NA	> 5	ND	>32	>32	>32
66a	S	4-NO_2-Ph	NA	NA	> 5	ND	>32	>32	>32
Compounds of Formula II									
6	O	Me	NA	NA	0.5	331	0.8	≤1	≤1
74b	O	Ph	NA	NA	0.7	222	ND	ND	ND
75b	O	3,4-$(OMe)_2$-Ph	NA	NA	2.5	250	1.4	ND	ND
63b	S	Me	NA	NA	0.3	134	1	4	≤1
64b	S	Ph	NA	NA	1.7	ND	1.3	4	≤1
62b	S	4-OMe-Ph	NA	NA	> 5	ND	5.5	16	3
65b	S	3,4-$(OMe)_2$-Ph	NA	NA	0.8	137	2.6	10	≤1
62c	S	4-OH-Ph	NA	NA	2.7	123	5.3	12	2
65c	S	3,4-$(OH)_2$-Ph	NA	NA	1.5	118	11	20	8
66b	S	4-NO_2-Ph	NA	NA	4.0	ND	2.5	ND	ND
Compounds of Formula III									
7	O	NA	8-OH	COMe	0.3	346	ND	ND	ND
45	S	NA	H	H	> 5	222	ND	ND	ND
81	S	NA	5-OCOMe	H	1.4	160	ND	ND	ND
82	S	NA	5-OH	H	1.0	117	ND	ND	ND
α-lapachone	NA	NA	NA	NA	10	ND	ND	ND	ND
β-lapachone	NA	NA	NA	NA	0.7	329	4	4	≤1
anthralin	NA	NA	NA	NA	0.7	294	NA	NA	NA
vehicle	NA	NA	NA	NA	NA	135	NA	NA	NA

[a]Antiproliferative activity against HaCaT cells. Inhibition of cell growth was significantly different with respect to that of the control, $N = 3$, $p < 0.05$. [b]Activity of LDH (mU) release in HaCaT cells after treatment with 2 μM test compound, $N = 3$, SD < 10%, $p < 0.05$. NA = not applicable. [c]Antiproliferative activity against colon cancer cell lines DLD1 and SW480 and breast cancer cell line MCF7. ND = not determined. NA = not applicable.

As shown in Table 1, treatment of HaCaT cells with anthralin was effective at inhibition of proliferation (IC_{50} = 0.7 μM) but caused substantial cellular damage, with LDH release significantly higher than vehicle controls. Similarly, β-lapachone and the 2-acetylated naphtho[2,3-b]furan-4,9-diones (compounds **6** and **7**) inhibited cell proliferation but caused significant LDH release as compared to vehicle. However, several of the thiophene analogs (compounds **63a, 64b, 65b, 65c, 81** and **82**) inhibited cell proliferation at concentrations comparable to β-lapachone and the furan analogs but without significant elevation of LDH release over the vehicle control.

Compounds of this invention were also effective at inhibiting proliferation of human cancer cells including cells from the colon cancer lines DLD1 and SW480 and from the breast cancer line MCF7. As shown in Table 1, IC_{50} values in the low micromolar range and below were obtained for several of these compounds in all three cancer cell lines

The similarity of their antiproliferative response to that of β-lapachone indicates that the present synthetic lapacho derivative compounds may be expected to show wide anticancer activity. β-lapachone has been shown to be active against breast cancer, leukemia, lung cancer, ovarian cancer, brain cancer, liver cancer, prostate cancer, and colorectal cancer. The lapacho derivatives of the present invention would also be effective in treating these disorders. These treatments may be accomplished utilizing the present lapacho derivative compounds (Formula I, II or III) alone or in combination with prior art chemotherapy agents or with radiation therapy. In a preferred embodiment the present lapacho derivative compounds are used for the treatment of cancer as a preventative drug by preventing cancer cell formation.

A variety of cancer cell lines are contemplated to determine the effectiveness of the novel lapacho derivatives of the present invention, including SK-OV-3 and OVCAR-3 human ovarian carcinoma cells; SW-480, HT-29 and HCT-116 human colon carcinoma cells; MCF-7 and MDA-MB-231 human breast carcinoma cells; MIA PACA-2 and BXPC-3 human pancreatic carcinoma cells; NCI-H226 and A549 human lung carcinoma cells; and DU-145 and PC-3 human prostate cancer cells. Since β-lapachone induces apoptosis only in cancer cell lines and not in normal cells (Li.,Y, et. al., PNAS, in press) the present compounds will also be tested in a

panel of normal cell lines including NCM 460 normal colonic epithelial cells and MCF 10A normal breast epithelial cells.

One potential effect of the present lapacho derivatives is induction of E2F1. Experiments have shown that β-lapachone induces sustained E2F1 activity in nuclei of cancer cells but not in normal cells, resulting in the arrest of cancer cells in G1 and/or S phase. The present lapacho derivatives would also be effective in sustaining E2F1 activity, thus causing G1 and/or S phase arrest. Furthermore, the present lapacho derivatives would have no significant toxic effects on normal cells.

The results of experiments with β-lapachone and similar chemical compounds have shown that the present lapacho derivatives would have a strong apoptotic effect on a variety of human cancer cells and that they can inhibit growth of other human cancer cells. The lack of toxic effects on normal cells at the concentrations needed for effectiveness against the cancer cells indicates that the present lapacho derivatives are very valuable chemotherapeutic reagents. It could be applied in many of the well-known methods currently used for chemotherapeutic treatment. For example, it may be injected directly into tumors, injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the cancer and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

Experimental Section

Melting points were determined with a Reichert Thermovar melting point apparatus and are uncorrected. Chromatography refers to column chromatography on silica gel (E. Merck, 70–230 mesh) using CH_2Cl_2 as eluant, unless otherwise stated. ^1H NMR spectra were recorded with a Varian EM 390 (90 MHz) or a Bruker Spectrospin WM 250 spectrometer (250 MHz), using tetramethylsilane as an internal standard. Fourier-transform IR spectra (KBr) were recorded on a Nicolet 510M FTIR spectrometer. UV spectra were recorded on a Kontron 810 spectrometer. Mass spectra (EI) were obtained on a Varian MAT 112S spectrometer (70 eV). Elemental Analysis were within ±0.4% of calculated values.

Compounds of Scheme 1

General Procedure for the Preparation of (R,S)-Naphtho[2,3-*b*]thiophen-2-yl-alkanols.

(R,S)-(4-Methoxyphenyl)-naphtho[2,3-*b*]thiophen-2-yl-methanol (62). To a solution of naphtho[2,3-*b*]thiophene (0.92 g, 4.99 mmol) in absolute Et_2O (80 mL) and tetramethylethylenediamine (0.08 mL, 0.8 mmol) was added *sec*-butyllithium (4.40 mL of a 1.3 M solution in hexane, 5.72 mmol) at -78 °C under N_2. Then the solution was stirred at -78 °C for 1 h. Dry 4-methoxybenzaldehyde (0.73 mL, 6.0 mmol), freshly distilled, was added at -78 °C, and the solution was allowed to warm to room temperature within 12 h. Then it was treated with a solution of half-saturated NH_4Cl (400 mL), the organic layer was washed with water (400 mL), dried over Na_2SO_4, and evaporated. The residue was purified by chromatography and recrystallized from CH_2Cl_2/hexane to afford white crystals: 72% yield; mp 164–165 °C; FTIR 3377 (OH), 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25–6.90 (m, 11H), 6.90 (d, 1H, ^3J = 4.01 Hz), 3.82 (s, 3H), 2.47 (d, 1H, ^3J = 4.01 Hz, exchangeable); MS *m/z* 320 (66, M^+), 135 (100). Anal. ($C_{20}H_{16}O_2S$) C, H.

(R,S)-Naphtho[2,3-*b*]thiophen-2-yl-ethanol (63) was obtained from naphtho[2,3-*b*]thiophene (1.00 g, 5.43 mmol) and acetaldehyde (0.37 mL, 6.52 mmol) as described for **62** to afford white needles: 44% yield; mp 182–184 °C; FTIR 3319 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.23–7.43 (m, 6H), 7.25 (s, 1H), 5.21 (qu, 1H, ^3J = 6.42 Hz), 1.82 (d, 1H, ^3J = 6.42 Hz, exchangeable), 1.69 (s, 3H). Anal. ($C_{14}H_{12}OS$) C, H.

(R,S)-Naphtho[2,3-*b*]thiophen-2-yl-phenylmethanol (64) was obtained from naphtho[2,3-*b*]thiophene (0.75 g, 4.07 mmol) and benzaldehyde (0.49 mL, 4.88 mmol) as described for **62** to afford white needles: 67% yield; mp 142–145 °C; FTIR 3319 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.56–7.16 (m, 12H), 6.13 (d, 1H, ^3J = 3.59 Hz), 2.58 (d, 1H, ^3J = 3.59 Hz, exchangeable). Anal. ($C_{19}H_{14}OS$) C, H.

(R,S)-(3,4-Dimethoxyphenyl)-naphtho[2,3-*b*]thiophen-2-yl-methanol (65) was obtained from naphtho[2,3-*b*]thiophene (1.00 g, 5.43 mmol) and 3,4-dimethoxybenzaldehyde (1.08 g, 6.51 mmol) as described for **62** to afford white crystals: 65% yield; mp 175–176 °C; FTIR 3481 (OH), 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.43–6.93 (m, 10H), 6.40 (d, 1H, ^3J = 3.00 Hz, exchangeable), 6.00 (d, 1H, ^3J = 3.00 Hz), 3.81 (s, 3H), 3.80 (s, 3H). Anal. ($C_{21}H_{18}O_3S$) C, H.

(R,S)-Naphtho[2,3-*b*]thiophen-2-yl-(4-nitrophenyl)methanol (66) was obtained from naphtho[2,3-*b*]thiophene (1.00 g, 5.43 mmol) and 4-nitrobenzaldehyde (1.07 g, 7.06 mmol) as

described for **62** to afford light-yellow crystals: 55% yield; mp 239–240 °C; FTIR 3548 (OH), 1596 cm^{-1}; ^1H NMR (DMSO-d_6) δ8.67–7.43 (m, 11H), 6.84 (d, 1H, ^3J = 4.31 Hz, exchangeable), 6.27 (d, 1H, ^3J = 4.31 Hz). Anal. ($C_{19}H_{13}NO_3S$) C, H.

General Procedure for the Preparation of Naphtho[2,3-*b*]thiophen-2-yl-alkanones. (4-Methoxyphenyl)-naphtho[2,3-*b*]thiophen-2-yl-methanone (62a). To a solution of **62** (1.00 g, 3.12 mmol) in CH_2Cl_2 (100 mL) was added activated MnO_2 (2.61 g, 30 mmol), and the mixture was stirred for 1.5 h, until the oxidation was completed (TLC control). The suspension was filtered, and the residue was washed with CH_2Cl_2 (3 × 200 mL). The solution was treated with hexane (500 mL), then concentrated, and the product was crystallized at -18 °C to afford lemon crystals: 81% yield; mp 211–212 °C; FTIR 1622 (CO), 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ8.43–7.01 (m, 11H), 3.92 (s, 3H); MS *m/z* 318 (100, M^+). Anal. ($C_{20}H_{14}O_2S$) C, H.

Naphtho[2,3-*b*]thiophen-2-yl-ethanone (63a) was obtained from **63** (0.35 g, 1.53 mmol) as described for **62a**, but it was stirred for 24 h to afford greenish-yellow needles: 84% yield; mp 224–225 °C; FTIR 1663 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ8.67–7.51 (m, 7H), 2.71 (s, 3H). Anal. ($C_{14}H_{10}OS$) C, H.

Naphtho[2,3-*b*]thiophen-2-yl-phenylmethanone (64a) was obtained from **64** (0.35 g, 1.21 mmol) as described for **62a** to afford yellow crystals: 96% yield; mp 164–165 °C; FTIR 1630 (CO), 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ8.42–7.45 (m, 12H). Anal. ($C_{19}H_{12}OS$) C, H.

(3,4-Dimethoxyphenyl)-naphtho[2,3-*b*]thiophen-2-yl-methanone (65a) was obtained from **65** (0.91 g, 2.60 mmol) as described for **62a** to afford lemon crystals: 87% yield; mp 175–176 °C; FTIR 1630 (CO), 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ8.44–6.97 (m, 10H), 4.00 (s, 3H), 3.98 (s, 3H). Anal. ($C_{21}H_{16}O_3S$) C, H.

Naphtho[2,3-*b*]thiophen-2-yl-(4-nitrophenyl)methanone (66a) was obtained from **66** (0.50 g, 1.49 mmol) as described for **62a** to afford orange crystals: 97% yield; mp 251–252 °C; FTIR 1628 (CO), 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ8.78–7.48 (m, 11H). Anal. ($C_{19}H_{11}NO_3S$) C, H.

General Procedure for the Oxidation of Naphtho[2,3-*b*]thiophenes to Naphtho[2,3-*b*]thiophene-4,9-diones. 2-(4-Methoxybenzoyl)-naphtho[2,3-*b*]thiophene-4,9-dione (62b). To a solution of **62a** (0.75 g, 2.35 mmol) in glacial acetic acid (50 mL) was added with stirring at room temperature, dropwise over 1 h, a solution of CrO_3 (0.66 g, 6.6 mmol) in glacial acetic acid (10 mL) and water (10 mL). The solution was stirred for an additional 30 min, then water (250 mL) was added, the product was filtered by suction, and purified by chromatography. The

combined fractions were treated with hexane, then concentrated, and the product was crystallized at -18 °C to afford lemon needles: 86% yield; mp 165–166 °C; FTIR 1667 (CO), 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ8.29–7.00 (m, 9H), 3.92 (s, 3H); MS *m/z* 348 (92, M^+), 135 (100). Anal. ($C_{20}H_{12}O_4S$) C, H.

2-Acetyl-naphtho[2,3-*b*]thiophene-4,9-dione (63b) was obtained from **63a** (0.18 g, 0.80 mmol) as described for **62b** to afford yellow crystals: 64% yield; mp 261–262 °C; FTIR 1669 (CO), 1651 (CO), 1590 cm^{-1}; ^1H NMR (DMSO-d_6) δ8.44 (s, 1H), 8.21–7.92 (m, 4H), 2.71 (s, 3H). Anal. ($C_{14}H_8O_3S$) C, H.

2-Benzoyl-naphtho[2,3-*b*]thiophene-4,9-dione (64b) was obtained from **64a** (0.35 g, 1.21 mmol) as described for **62b** to afford yellow crystals: 70% yield; mp 158–159 °C; FTIR 1667 (CO), 1652 (CO), 1634 (CO), 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ8.30–7.53 (m, 10H). Anal. ($C_{19}H_{10}O_3S$) C, H.

2-(3,4-Dimethoxybenzoyl)-naphtho[2,3-*b*]thiophene-4,9-dione (65b) was obtained from **65a** (0.57 g, 1.63 mmol) as described for **62b** to afford orange-yellow needles: 48% yield; mp 212–218 °C; FTIR 1669 (CO), 1629 (CO), 1593 cm^{-1}; ^1H NMR (DMSO-d_6) δ8.19–7.18 (m, 8H), 3.91 (s, 3H), 3.86 (s, 3H). Anal. ($C_{21}H_{14}O_5S$) C, H.

2-(4-Nitrobenzoyl)-naphtho[2,3-*b*]thiophene-4,9-dione (66b) was obtained from **66a** (0.30 g, 0.90 mmol) as described for **62b** to afford lemon needles: 76% yield; mp 270 °C; FTIR 1671 (CO), 1640 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ8.46–7.81 (m, 9H). Anal. ($C_{19}H_9NO_5S$) C, H.

General Procedure for the Cleavage of Methyl Ethers. 2-(4-Hydroxybenzoyl)-naphtho[2,3-*b*]thiophene-4,9-dione (62c). To a solution of **62b** (0.25 g, 0.72 mmol) in dry CH_2Cl_2 (50 mL) was added BBr_3 (0.70 mL, 7.18 mmol) at room temperature under N_2, and the solution was stirred at room temperature for 120 h. Then 2 N HCl (100 mL) was added, the organic layer was extracted with 2 N NaOH (3 × 100 mL), the combined aqueous layer was acidified with conc. HCl, and the product was dissolved in ethyl acetate. The organic layer was washed with a saturated solution of NaCl, then concentrated, and the product was crystallized at -18 °C to afford yellow-green crystals: 46% yield; mp 264–265 °C; FTIR 3553 (OH), 1669 (CO), 1648 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ10.66 (s, 1H, exchangeable), 8.19–6.96 (m, 9H). Anal. ($C_{19}H_{10}O_4S$) C, H.

2-(3,4-Dihydroxybenzoyl)-naphtho[2,3-*b*]thiophene-4,9-dione (65c) was obtained from **65b** (0.20 g, 0.53 mmol) as described for **62c**. Recrystallization from toluene/ethyl acetate afforded

orange-yellow crystals: 65% yield; mp 272–274 °C dec; FTIR 3448 (OH), 3309 (OH), 1671 (CO), 1632 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.0–9.0 (s, 2H, exchangeable), 8.20–6.93 (m, 8H). Anal. ($C_{19}H_{10}O_5S$) C, H.

General Procedure for the Preparation of (R,S)-Naphtho[2,3-*b*]furan-2-yl-alkanols. (R,S)-Naphtho[2,3-*b*]furan-2-yl-ethanol (73). To a solution of naphtho[2,3-*b*]furan (0.50 g, 2.96 mmol) in absolute Et_2O (50 mL) and tetramethylethylenediamine (0.15 mL, 1.5 mmol) was added *sec*-butyllithium (5.50 mL of a 1.3 M solution in hexane, 7.15 mmol) at -78 °C under N_2, and the solution was stirred at -78 °C for 4 h. Dry acetaldehyde (0.13 mL, 3.84 mmol), freshly distilled, was added at -78 °C, and the solution was allowed to warm to room temperature within 12 h. Then it was treated with a half-saturated solution of NH_4Cl (250 mL), the organic layer was washed with water (250 mL), dried over Na_2SO_4, and evaporated. The residue was purified by chromatography and recrystallized from CH_2Cl_2/hexane to afford white needles: 65% yield; mp 165–167 °C; FTIR 3313 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99–7.19 (m, 6H), 6.72 (s, 1H), 5.6 (qu, 1H, ^3J = 6.6 Hz), 2.09 (s, 1H, exchangeable), 1.68 (d, 3H, ^3J = 6.6 Hz). Anal. ($C_{14}H_{12}O_2$) C, H.

(R,S)-Naphtho[2,3-*b*]furan-2-yl-phenylmethanol (74) was obtained from naphtho[2,3-*b*]furan (0.32 g, 1.89 mmol) and benzaldehyde (0.25 mL, 2.46 mmol) as described for **73**. Recrystallization from hexane afforded white crystals: 42% yield; mp 100–101 °C; FTIR 3382 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96–7.32 (m, 11H), 6.65 (s, 1H), 5.98 (d, 1H, ^3J = 4.09 Hz), 2.58 (d, 1H, ^3J = 4.09 Hz, exchangeable). Anal. ($C_{19}H_{14}O_2$) C, H.

General Procedure for the Preparation of Naphtho[2,3-*b*]furan-2-yl-alkanones. Naphtho[2,3-*b*]furan-2-yl-ethanone (73a) was obtained from **73** (0.20 g, 0.94 mmol) as described for **62a**, but it was stirred for 12 h to afford greenish needles: 81% yield; mp 193 °C dec (lit (Garuti et al. *Farmaco Ed. Sci.* **38**: 527-532, 1983) 180 °C); FTIR 1679 (CO), 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.23–7.42 (m, 7H), 2.67 (s, 3H). Anal. ($C_{14}H_{10}O_2$) C, H.

Naphtho[2,3-*b*]furan-2-yl-phenylmethanone (74a) was obtained from **74** (0.18 g, 0.66 mmol) as described for **62**. Recrystallization from hexane afforded yellow needles: 86% yield; mp 140–142 °C (lit (Sen and Saxena, *J. Indian Chem. Soc.* **36**: 283-284, 1959) 101 °C); FTIR 1634 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25–7.43 (m, 12H). Anal. ($C_{19}H_{12}O_2$) C, H.

(3,4-Dimethoxyphenyl)-naphtho[2,3-*b*]furan-2-yl-methanone (75a) was obtained from naphtho[2,3-*b*]furan (0.20 g, 1.18 mmol) and 3,4-dimethoxybenzaldehyde (0.26 g, 1.54 mmol) as

described for **73**, and the crude product was oxidized as described for **62a**. Recrystallization from hexane afforded light-yellow crystals: 61% yield; mp 155–157 °C; FTIR 1644 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ8.25 (s, 1H), 8.04 (s, 1H), 7.80–6.99 (m, 8H), 4.01 (s, 3H), 4.00 (s, 3H). Anal. ($C_{21}H_{16}O_4$) C, H.

General Procedure for the Preparation of 2-Acyl-naphtho[2,3-*b*]furan-4,9-diones. 2-Acetyl-naphtho[2,3-*b*]furan-4,9-dione (6) was obtained from **73a** (0.11 g, 0.80 mmol) as described for **62b**. Recrystallization from CH_2Cl_2/hexane afforded yellow crystals: 48% yield; mp 229–230 °C (lit (Lopez et al. *J. Heterocycl. Chem.* **21**: 621-622, 1984) 222–224 °C); FTIR 1692 (CO), 1674 (CO), 1582 cm^{-1}; ^1H NMR ($CDCl_3$) δ8.29–7.92 (m, 4H), 7.61 (s, 1H), 2.67 (s, 3H). Anal. ($C_{14}H_8O_4$) C, H.

2-Benzoyl-naphtho[2,3-*b*]furan-4,9-dione (74b) was obtained from **74a** (0.05 g, 0.18 mmol) as described for **62b** to afford yellow needles: 44% yield; mp 198–200 °C; FTIR 1674 (CO), 1659 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ8.30–7.54 (m, 10H). Anal. ($C_{19}H_{10}O_4$) C, H.

2-(3,4-Dimethoxybenzoyl)-naphtho[2,3-*b*]furan-4,9-dione (75b) was obtained from **75a** (0.16 g, 0.48 mmol) as described for **62b**. Recrystallization from CH_2Cl_2/hexane afforded lemon crystals: 40% yield; mp 242–243 °C; FTIR 1676 (CO), 1638 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31–7.00 (m, 8H), 4.01 (s, 3H), 4.00 (s, 3H). Anal. ($C_{21}H_{14}O_6$) C, H.

Compounds of Scheme 2

2-Hydroxy-6-(2-thenoyl)-benzoic acid (77). To a suspension of 3-hydroxyphthalic anhydride (1.00 g, 6.09 mmol) and $AlCl_3$ (2.44 g, 18.27 mmol) in absolute CH_2Cl_2 (20 mL) and tetramethylethylenediamine (0.15 mL, 1.5 mmol) a solution of thiophene (0.49 mL, 6.10 mmol) in absolute CH_2Cl_2 (10 mL) was added dropwise over 30 min such that the temperature of the reaction remained below 30 °C. The solution was stirred at room temperature for an additional 12 h. Then it was treated with ice-water (250 mL), and the product was extracted with CH_2Cl_2 (5 × 100 mL). Charcoal was added to the combined organic layer, the mixture was filtered, extracted with 2 N NaOH (3 × 50 mL) and then acidified with conc. HCl to afford white crystals: 58% yield; mp 168–170 °C; FTIR 3432 (OH), 3151, 1681 (CO_2H), 1630 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ11.45 (s, br, 1H, exchangeable), 8.40 (dd, 1H, ^3J = 4.95 Hz, ^4J = 1.21 Hz), 7.52 (dd, 1H, ^3J = 8.35 Hz, ^3J = 7.43 Hz), 7.39 (dd, 1H, ^3J = 3.79 Hz, ^4J = 1.21 Hz), 7.21 (dd, 1H, ^3J = 4.95 Hz, ^3J = 3.79 Hz), 7.13 (dd, 1H, ^3J = 8.35 Hz, ^4J = 1.09 Hz), 6.97 (dd, 1H, ^3J = 7.43 Hz, ^4J

= 1.09 Hz). Anal. ($C_{12}H_8O_4S$) C, H.

2-Hydroxy-6-(2-thenyl)-benzoic acid (78). To a mixture of zinc dust (3.55 g, 54.3 mmol) and $CuSO_4 \cdot 5\ H_2O$ (0.10 g) in conc. aqueous NH_3 (250 mL) was added **77** (1.39 mL, 5.60 mmol). The reaction mixture was heated to reflux for 24 h, then filtered while hot, cooled to room temperature, acidified with conc. HCl, and crystallization was completed overnight in an ice-bath to afford white needles: 73% yield; mp 155–158 °C; FTIR 3427 (OH), 3290–2620 (CO_2H), 1654 (CO_2H) cm^{-1}; ^1H NMR (DMSO-d_6) δ11.70 (s, br, 1H, exchangeable), 10.50 (s, br, exchangeable), 7.29 (dd, 1H, ^3J = 5.13 Hz, ^4J = 1.27 Hz), 7.24–7.18 (m, 1H), 6.89 (dd, 1H, ^3J = 5.13 Hz, ^3J = 3.42 Hz), 6.81–6.71 (m, 3H), 4.22 (s, 2H). Anal. ($C_{12}H_{10}O_3S$) C, H.

4,5-Diacetoxy-naphtho[2,3-*b*]thiophene (80). A mixture of **78** (0.50 g, 2.13 mmol), acetic anhydride (5 mL), glacial acetic acid (12.5 mL), and anhydrous $ZnCl_2$ (0.20 g, 2.13 mmol) was heated to reflux for 2 h. Then the reaction was cooled to room temperature and treated with water (100 mL). The product was filtered by suction, dissolved in CH_2Cl_2, purified by chromatography and recrystallized from CH_2Cl_2/hexane to afford pale yellow needles: 33% yield; mp 208–209 °C; FTIR 1759 (ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ8.32 (s, 1H), 7.86–7.11 (m, 5H), 2.50 (s, 3H), 2.44 (s, 3H). Anal. ($C_{16}H_{12}O_4S$) C, H.

5-Acetoxy-naphtho[2,3-*b*]thiophene-4,9-dione (81) was obtained from **80** (0.10 g, 0.33 mmol) as described for **62b**. In addition, the mother liquor was extracted with CH_2Cl_2 (30 mL), the organic layer washed with water (3 × 50 mL), the product was purified by chromatography using CH_2Cl_2/hexane (3/1) and recrystallized from CH_2Cl_2/hexane to afford bright-yellow needles: 55% yield; mp 210 °C; FTIR 1752 (ester), 1666 (CO), 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ8.23 (dd, 1H, ^3J = 7.75 Hz, ^4J = 1.31 Hz), 7.76 (dd, 1H, ^3J = 8.08 Hz, ^3J = 7.75 Hz), 7.73 (d, 1H, ^3J = 5.08 Hz), 7.64 (d, 1H, ^3J = 5.08 Hz), 7.39 (dd, 1H, ^3J = 8.08 Hz, ^4J = 1.31 Hz), 2.49 (s, 3H). Anal. ($C_{14}H_8O_4S$) C, H.

5-Hydroxy-naphtho[2,3-*b*]thiophene-4,9-dione (82). A solution of **81** (0.03 g, 0.11 mmol) in CH_2Cl_2 (10 mL) and 6 N NaOH was heated to reflux for 12 h, until the yellow solution turned into deep violet. Then the reaction mixture was poured into ice-water (50 mL), acidified with conc. HCl, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layer was dried over Na_2SO_4, purified by chromatography and recrystallized from hexane to afford orange crystals: 92% yield; mp 199–200 °C; FTIR 3440 (OH), 1656 (CO), 1632 (CO···HO) cm^{-1}; ^1H NMR ($CDCl_3$) δ12.36 (d, 1H, ^5J = 0.44 Hz), 7.79 (dd, 1H, ^3J = 7.47 Hz, ^4J =

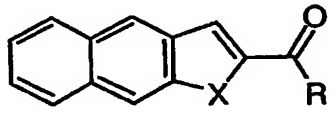
1.20 Hz), 7.76 (d, 1H, ^3J = 5.08 Hz), 7.70 (d, 1H, ^3J = 5.08 Hz), 7.63 (m, 1H, ^3J = 7.47 Hz, ^3J = 8.42 Hz, ^5J = 0.44 Hz), 7.29 (dd, 1H, ^3J = 8.42 Hz, ^4J = 1.21 Hz). Anal. ($C_{12}H_6O_3S$) C, H.

Biological Assay Methods. HaCaT keratinocyte proliferation assay and LDH release were described previously in full detail (Müller et al. *J. Med. Chem.* **39**: 3132-3138, 1996; Müller et al. *J. Med. Chem.* **37**: 1660-1669, 1994). For the cancer cell line studies, exponentially growing cells were seeded at 1,000 cells per well in six-well plates and allowed to attach for 24h. Compounds of the invention or β-lapachone, solubilized in DMSO, were added to the wells in micromolar concentrations. Control wells were treated with equivalent volumes of DMSO. After 4h the supernatant was removed and fresh medium was added. Cultures were observed daily for 10-15 days and then were fixed and stained. Colonies of greater than 30 cells were scored as survivors.

CLAIMS

We claim:

1. A compound of formula I:



I

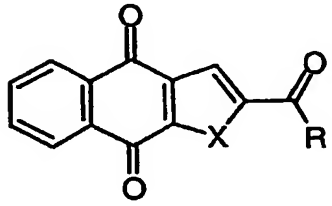
or a pharmaceutically acceptable salt thereof or a regioisomeric mixture thereof, wherein X is O or S; and R is straight-chained or branched alkyl having 1-6 carbons, aryl, substituted aryl, or straight-chained or branched alkylaryl.

2. A compound according to claim 1, wherein X is S, and R is aryl or substituted aryl.

3. A compound according to claim 1 or 2, wherein said substituted aryl may be substituted with hydroxyl, alkoxy, alkyl, nitro, halogen, carboxyl or carboxyalkyl.

4. A compound according to claim 1, wherein X is S, and R is phenyl.

5. A compound of formula II:



II

or a pharmaceutically acceptable salt thereof or a regioisomeric mixture thereof wherein X is O or S; and R is straight-chained or branched alkyl having 1-6 carbons, aryl, substituted aryl, or straight-chained or branched alkylaryl.

6. A compound according to claim 5, wherein X is O or S, and R is alkyl, aryl or mono- or di-substituted aryl.

7. A compound according to claim 5 or 6, wherein said substituted aryl may be substituted with hydroxyl, alkoxy, alkyl, nitro, halogen, carboxyl or carboxyalkyl.

8. A compound according to claim 5, wherein X is O, and R is phenyl.

9. A compound according to claim 5, wherein X is O, and R is 3,4-dimethoxyphenyl.

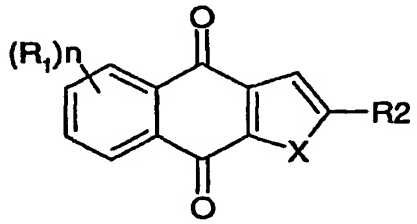
10. A compound according to claim 5, wherein X is S, and R is phenyl.

11. A compound according to claim 5, wherein X is S, and R is 3,4-dimethoxyphenyl.

12. A compound according to claim 5, wherein X is S, and R is 4-hydroxyphenyl.

13. A compound according to claim 5, wherein X is S, and R is 3,4-dihydroxyphenyl.

14. A compound of formula III:



III

or a pharmaceutically acceptable salt thereof or a regioisomeric mixture thereof, wherein X is O or S; R_1 is independently at each incidence hydrogen, hydroxyl, alkoxyl, alkyl having 1-6 carbons, nitro, halogen, carboxyl or carboxyalkyl; R_2 is hydrogen, acyl, straight-chained or branched alkyl of 1-6 carbons or carboxyalkyl; and n is 0, 1 or 2.

15. A compound according to claim 14, wherein X is S, R_1 is hydroxyl or alkylcarbonyl, R_2 is hydrogen, and n is 1 or 2.

16. A compound according to claim 14, wherein X is S, R_1 is 5-carboxymethyl, R_2 is hydrogen, and n is 1.

17. A compound according to claim 14, wherein X is S, R_1 is 5-hydroxyl, R_2 is hydrogen, and n is 1.

18. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 in combination with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 4 in combination with a pharmaceutically acceptable carrier.

20. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 5 in combination with a pharmaceutically acceptable carrier.

21. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 8-13 in combination with a pharmaceutically acceptable carrier.

22. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 14 in combination with a pharmaceutically acceptable carrier.

23. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claims 16 or 17 in combination with a pharmaceutically acceptable carrier.

24. A method of treating or preventing cell proliferative disorders comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition that induces sustained elevation of E2F activation in tumor cells without affecting E2F levels in normal cells.

25. The method according to claim 24, comprising the pharmaceutical composition of claim 18.

26. The method according to claim 24, comprising the pharmaceutical composition of claim 19.

27. The method according to claim 24, comprising the pharmaceutical composition of claim 20.

28. The method according to claim 24, comprising the pharmaceutical composition of claim 21.

29. The method according to claim 24, comprising the pharmaceutical composition of claim 22.

30. The method according to claim 24, comprising the pharmaceutical composition of claim 23

31. A method of treating cancer or precancerous conditions or to prevent cancer comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 18.

32. A method of treating cancer or precancerous conditions or to prevent cancer comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 19.

33. A method of treating cancer or precancerous conditions or to prevent cancer comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 20.

34. A method of treating cancer or precancerous conditions or to prevent cancer comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 21.

35. A method of treating cancer or precancerous conditions or to prevent cancer comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 22.

36. A method of treating cancer or precancerous conditions or to prevent cancer comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 23.

37. A method of treating or preventing psoriasis comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 18.

38. A method of treating or preventing psoriasis comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 19.

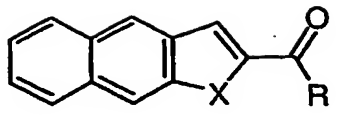
39. A method of treating or preventing psoriasis comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 20.

40. A method of treating or preventing psoriasis comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 21.

41. A method of treating or preventing psoriasis comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 22.

42. A method of treating or preventing psoriasis comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition according to claim 23.

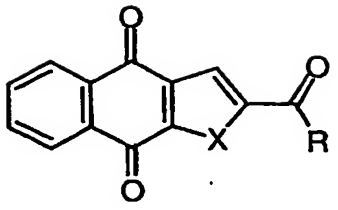
Figure 1



I

Compound	X	R
73a	O	Me
74a	O	Ph
75a	O	3,4-$(OMe)_2$-Ph
63a	S	Me
64a	S	Ph
62a	S	4-OMe-Ph
65a	S	3,4-$(OMe)_2$-Ph
66a	S	4-NO_2-Ph

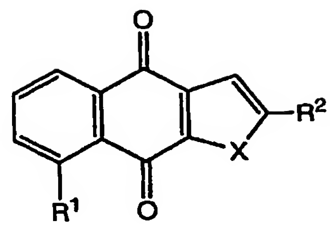
Figure 2



II

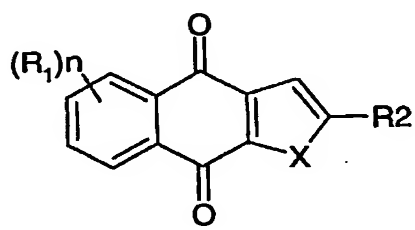
Compound	X	R
6	O	Me
74b	O	Ph
75b	O	3,4-$(OMe)_2$-Ph
63b	S	Me
64b	S	Ph
62b	S	4-OMe-Ph
65b	S	3,4-$(OMe)_2$-Ph
62c	S	4-OH-Ph
65c	S	3,4-$(OH)_2$-Ph
66b	S	4-NO_2-Ph

Figure 3A



Compound	X	R[1]	R[2]
7	O	OH	COMe

Figure 3B



III

Compound	X	R[1]	R[2]
45	S	H	H
81	S	5-OCOMe	H
82	S	5-OH	H

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